IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Audrey Goddard et al.	Examiner:	Lorraine Spector
Serial No.:	09/202,054	Group Art Unit:	1647
Filed:	December 7, 1998	Docket:	G&C 669.23-US-WO
Title:	ANTIBODIES TO HUMAN TOLL HOMOLOGUES		

PRE-APPEAL BRIEF REQUEST FOR REVIEW

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Office Action dated November 25, 2005, Applicants hereby submit a Notice of Appeal accompanied by a Pre-Appeal Brief Request for Review. The claims have not been amended.

Appellants traverse the rejections for one or more of the following reasons:

(1) The disclosure in WO 91/09614 fails to teach or suggest an isolated antibody which binds to a PRO285 polypeptide comprising amino acids 1 to 1049 encoded by SEQ ID NO:2 or an isolated antibody which binds to residues 20 to 836 of SEQ ID NO:1.

(2) The Patent Office fails to provide evidence sufficient to show that Appellants' statements of asserted utility would be considered "false" by a person of ordinary skill in the art.

Independent claims 28, 48 and 55 are directed to isolated antibodies that bind a PRO285 polypeptide comprising amino acids 1 to 1049 encoded by SEQ ID NO:2 or residues 20 to 836 of SEQ ID NO:1.

Appellants submit that based on the claims, the disclosure in the cited art, and the legal requirements for a finding of a lack of utility, there are clear errors in the Patent Office's rejections and further, the rejections fail to establish essential elements needed for a prima facie rejection of the pending claims.

1. *Failure to Establish Prima Facie Case under 35 U.S.C. §102(b) and 103(a)*

Appellants directs the panel to pages 5-7 of the Amendment filed by Appellant on September 12, 2005 for the substance of the arguments. Based on such arguments, Appellants submit that there is clear error in the Patent Office's rejection.

WO 91/09614 to Ruggeri et al., discloses a 19 residue platelet membrane glycoprotein Ib peptide having a 9 amino acid segment that matches a 9 amino acid segment of PRO285 amino acid residues. In view of this sequence identity, the Patent Office states "one would reasonably expect an antibody raised

against Ruggeri's peptide to bind to PRO285" (Office Action dated October 26, 2004), that this is anticipation via inherency and that "[I]t is not necessary that Ruggeri have any knowledge of PRO285 for anticipation to be found" (Office Action dated June 9, 2003).

Appellants disagree because it is known in the art that polypeptides such as the 806 and 1049 amino acid PRO 285 polypeptides recited in claim 55 do not exhibit a two-dimensional structure where every single amino acid residue (or 9 amino acid segment) is able to contact proteins such as antibodies. Instead, polypeptides are known to fold in three dimensions and the three-dimensional conformation of a polypeptide dictates which potentially antigenic determinants are either: (1) exposed at the exterior of the polypeptide and capable of being bound by antibodies; or (2) hidden in the interior of the polypeptide and inaccessible to antibodies.

The 9 amino acids in PRO 285 that have identity to the 9 residue segment in platelet membrane glycoprotein Ib peptide disclosed in Ruggeri occur at positions 704-712, a region in PRO 285 that is flanked on either side by hundreds of other amino acid residues recited in the claims. As is known in the art, these hundreds of flanking PRO 285 amino acid residues may assume a three-dimensional conformation that physically prevents antibodies raised against the platelet membrane glycoprotein Ib peptide from contacting this segment of 9 amino acids in PRO 285. The Ruggeri disclosure however fails to provide the information that allows an artisan to discern whether this does or does not occur.

While the Patent Office asserts that the Ruggeri disclosure anticipates the claimed invention via inherency because "it would be more likely than not" that an antibody raised against Ruggeri's peptide to bind to PRO285 (Office Action dated November 25, 2005), Appellants respectfully note that the Patent Office's conjecture as to what an antibody raised against Ruggeri's peptide will or will not bind is an improper basis for a finding of anticipation. In particular, courts find that "anticipation of a claimed product cannot be predicated on mere conjecture as to the characteristics of a prior art product". See, e.g. *Ex parte* Standish, 10 USPQ2d 1454, 1457 (Bd. Pat. App. & Int'f 1989). Instead, courts find that a claim is anticipated only if each and every element set forth in the claim is found in a prior art reference. See, e.g. *Verdegaal Bros. V. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The prohibition on using conjecture as a basis for a finding of anticipation is further articulated in the case law pertaining to anticipation via inherency. In particular, when articulating the legal requirements for a finding of anticipation via inherency, courts state that inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." See, e.g. M.P.E.P. 2112 and *Continental Can Co. v. Monsanto Co.*, 20 USPQ 2d 1746, 1749 (Fed. Cir. 1991). Instead, to establish inherency, the extrinsic evidence "must make clear that the missing

descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co.*, 20 USPQ 2d 1749. The Patent Office's assertion that antibody cross-reactivity "would be more likely than not" demonstrates that the disclosure in WO 91/09614 is not sufficient to allow one of skill in the art to determine whether the cross-reactivity is necessarily present. Consequently, the disclosure in WO 91/09614 cannot anticipate the claimed invention via inherency. For these reasons, based upon the claims and the cited art, there are clear errors in the Patent Office's rejection and further, the rejections fail to establish the elements needed for a prima facie rejection under 35 U.S.C. §102(b).

As the disclosure in WO 91/09614 is used in the Patent Office's determination that the claimed subject matter would have been obvious to the artisan, there are also clear errors in the Patent Office's rejection and further, the rejections fail to establish the elements needed for a prima facie rejection under 35 U.S.C. §103(a).

2. *Failure to Establish Prima Facie Case under 35 U.S.C. §101 and 112, First Paragraph.*

Appellants directs the panel to pages 2-5 of the Amendment filed by Appellant on September 12, 2005 for the substance of the arguments. Based on such arguments, Appellants submit that there is clear error in the Patent Office's rejections.

Appellants' disclosure relating to the utility of the claimed subject matter teaches that comparative homology analyses and functional data from Toll family members indicate that PRO285 polypeptide signaling activates NF-κB, an event which leads to the expression of the inflammatory cytokines IL-1, IL-6 and IL-8. See, e.g. page 13, lines 13-25. Appellants' disclosure further teaches that antibodies to the PRO285 polypeptide can act as agonists or antagonists of NF-κB signaling and can therefore be used in methods designed to modulate the expression of genes controlled by NF-κB. See, e.g. page 13, lines 6-25. As is known in the art, methods designed to modulate the expression of IL-1, IL-6 and IL-8 (e.g. via NF-κB activation) can be used in a variety of contexts. For example, reagents which induce the expression of IL-1, IL-6 and IL-8 are used in the topical treatment of warts. The specification further teaches that antagonistic anti-PRO285 antibodies may be used in pathologies characterized by an overexpression of IL-1, IL-6 and IL-8 (i.e. septic shock). See, e.g., page 37, lines 10-29. Consequently, the asserted utility of the claimed anti-PRO 285 antibodies is based for example upon the Appellants' understanding that (1) PRO285 polypeptide signaling modulates NF-κB activity; (2) antibodies specific for this receptor can modulate this activity; (3) the modulation of NF-κB modulates the expression of the inflammatory cytokines IL-1, IL-6 and IL-8; and (4) pathologies such as septic shock and warts are treated via the modulation of IL-1, IL-6 and IL-8 expression.

The use of an antibody to modulate the signaling of a receptor whose biological activity is associated with a pathological syndrome conforms to established scientific principles and is the principle upon which a significant number of therapeutic regimens are based. In the instant case, the association of PRO285 with NF-κB signaling via homology analyses is an art accepted method known to identify a function associated with a specific amino acid sequences. The use of agonistic and antagonistic antibodies as reagents to modulate the biological activities of a target receptor (e.g. NF-κB signaling) is also well known and accepted practice in the art. It is also known in the art that NF-κB controls the expression of IL-1, IL-6 and IL-8, cytokines whose aberrant expression is observed in a number of pathological syndromes including septic shock. Because the utility asserted by the Appellants is based upon established scientific principles, one of skill in the art would not, as the Patent Office asserts, be considered "false" by a person of ordinary skill in the art. To illustrate this, Appellants provided an opinion of a qualified expert stating that one of skill in the art would find credible Appellants teaching that PRO285 can induce the expression of that IL-1, IL-6 and IL-8 (NF-κB-controlled genes) and that antibodies to PRO285 can be made and used in accordance with routine techniques to modulate the expression of these inflammatory cytokines. For these reasons, Appellants' asserted utility for the claimed subject matter: (1) is readily understood by a skilled artisan; (2) conforms to scientific principles; and (3) is acknowledged in opinion from a qualified expert.

Applicants enjoy a presumption that an asserted utility is true. In order to overcome this presumption of truth that an applicant enjoys, Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered "false' by a person of ordinary skill in the art. The evidence provided by the Patent Office fails to meet this burden. For example, one of skill in the art would not, as the Patent Office Asserts, disregard the expert opinion regarding the significance of Appellants' homology analysis because "of the six essential residues for IL-R1 signaling domain, only two are conserved in PRO285" (Office Action dated March 15, 2004). Instead, one of skill in the art would note that while only 2 of the 13 essential residues are identical, homology analysis in this art are not limited to comparisons of identical amino acid residues but also include comparisons of amino acids having conserved (i.e. chemically similar) side chain properties (see Amendment filed by Appellant December 9, 2003 and pages 5-6 of the Amendment filed by Appellant on July 15, 2004). Similarly, because it is known in the art that NF-κB controls the expression of IL-1, IL-6 and IL-8, cytokines whose aberrant expression is observed in a pathological syndromes including septic shock, Appellants provide a reasonable correlation between the activity and the asserted use. Consequently, no further correlation is required (e.g. as asserted in the Office Action dated November 25, 2005).

As noted in M.P.E.P. §2107.02, where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong" even when there may be reason to believe that an assertion is not entirely accurate. Instead, an assertion of utility is to be considered credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion. As noted above, neither situation occurs in Appellants' asserted utility. In addition, the Patent Office fails to provide evidence sufficient to show that the statement of asserted utility would be considered "false' by a person of ordinary skill in the art. Consequently, the legal presumption that Appellants statement of utility is true has not been overcome. For these reasons, based upon the claims and the asserted utility, there are clear errors in the Patent Office's rejection and further, the rejections fail to establish the elements needed for a prima facie rejection under 35 U.S.C. §101.

The Patent Office also asserts that because the claimed invention is not supported by either a specific, substantial and credible asserted utility, one skilled in the art clearly would not know how to use the claimed invention, and therefore this invention is not enabled. As noted above, the Patent Office has failed to provide evidence sufficient to show that the statement of asserted utility would be considered "false" by a person of ordinary skill in the art, and one skilled in the art clearly would in fact know how to use the claimed invention without undue experimentation. For these reasons, based upon the claims and the asserted utility, there are clear errors in the Patent Office's rejection and further, the rejections fail to establish the elements needed for a prima facie rejection under 35 U.S.C. §101.

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Patent Office believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicant's undersigned attorney.

Respectfully submitted,

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